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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,414	06/27/2001	Mark E Gurney	29915/6280M	2436

7590 09/05/2003

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	13

DATE MAILED: 09/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,414	GURNEY ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *151-200* is/are pending in the application.

4a) Of the above claim(s) *170-200* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *151-169* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *151-200* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 4 in Paper No. 7 (29 May 2003) is acknowledged. The traversal is on the ground(s) that if the product is found allowable that groups 9, 11, and 12 be rejoined. This is not found persuasive because at the present time, no claims are in condition for allowance. However, the Examiner notes that the Applicant is correct and that upon reaching allowable subject matter, rejoinder will be considered. The requirement is still deemed proper and is therefore made FINAL.

2. Newly submitted claims 170-200 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant elected Group 4 (claims 47-54, 58-60, 62-70, and 142) drawn in part to a method for producing a polypeptide comprising SEQ ID NO: 4 comprising polynucleotides, vectors, and host cells comprising same, and the polypeptide comprising SEQ ID NO: 4 in Paper No. 7 (29 May 2003) with traverse. Claims 150-169 are directed to this originally elected invention and therefore are under examination.

3. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 170-200 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of Application, Amendments, and/or Claims

4. The Amendments filed 29 May 2003 (Paper No. 7) and 19 June 2003 (Paper No. 10) have been received and entered in full. Claims 1-150 have been cancelled and claims 151-200 have been added.

5. The Declaration of Michael Bienkowski, Ph.D. under 37 CFR 1.132 filed 29 May 2003 (Paper No. 11) has been received and entered. However, since no rejections have been set forth in the instant Application and the Applicant has not put forth any reasons for the Declaration to be filed, the information contained therein has not been considered.

Information Disclosure Statement

6. The information disclosure statement filed 19 June 2003 (Paper No. 11) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Applicant is invited to provide replacement copies of the references listed therein with the response to this Office Action at no additional cost.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a). An incorrect Application No. and Attorney Docket No. are listed on the instant declaration.

The oath or declaration also incorrectly claims domestic priority to provisional applications 60/101594 filed 24 September 1998 and 60/155493 filed 23 September 1999. This contradicts the current USPTO which lists the instant Application as a 371 National Stage filing of PCT/IB01/00797. Appropriate correction is required.

Provisional Obvious Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims **151, 155, 161, and 162** are provisionally rejected under the judicially created doctrine of double patenting over claims 1, 3, 21, and 22 of copending Application No. 09/795847 (herein cited as US Patent Application Publication US 2001/0018208 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the polynucleotide of Application No. 09/795847 shares 99.9% sequence homology with SEQ ID NO: 3 and the polypeptide of Application No. 09/795847 shares 99.7% sequence homology with SEQ ID NO: 4 thus meeting the limitations of claims 151, 155, 161, and 162. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

9. Claim **151** is provisionally rejected under the judicially created doctrine of double patenting over claim 1 of copending Application No. 09/794743 (herein cited as US Patent Application Publication US 2001/0021391 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the polypeptide of Application No. 09/795847 shares 99.7% sequence homology with SEQ ID NO: 4 thus meeting the limitations of claim 151. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims **151-169** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a purified polypeptide comprising SEQ ID NO: 4, a purified polynucleotide comprising SEQ ID NO: 3, vectors, expression vectors, and host cells comprising same* does not reasonably provide enablement for *polypeptides that are at least 95% identical to a fragment of SEQ ID NO: 4, continuous fragments, fragments thereof, or polynucleotides which hybridize to the complement of SEQ ID NO: 3 and fragments thereof.* The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

11. The claims are drawn very broadly to fragments, derivatives, and variants of SEQ ID NO: 3 and SEQ ID NO: 4, as well as vectors and host cells comprising said fragments, derivatives, and variants of SEQ ID NO: 3. The language of said claims encompass all polypeptides for which a least some fragment thereof shares 95% sequence homology with SEQ ID NO: 4.

12. The specification teaches that SEQ ID NO: 3 encodes SEQ ID NO: 4, an Asp2 protein.

13. The specification fails to provide any guidance for the successful isolation, cloning, and expression of fragments, derivatives, and variants of SEQ ID NO: 3 and SEQ ID NO: 4, and since resolution of the various complications in regards to expressing and using proteins based solely on sequence homology is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known Asp2 proteins to correlate with fragments, derivatives, and variants of SEQ ID NO: 3 and SEQ ID NO: 4. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

14. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide structure and function based solely on sequence homology is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of making the claimed fragments, derivatives, and variants of SEQ ID NO: 3 and

SEQ ID NO: 4, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

15. The following references are cited herein to illustrate the state of the art of protein biochemistry and Asp2 proteins.

16. On the nature of the invention, Tanahashi and Tabira (2001) "Three novel alternatively spliced isoforms of the human beta-site amyloid precursor protein cleaving enzyme (BACE) and their effect on amyloid beta-peptide production." Neuroscience Letters **307**: 9-12 teach that changes in BACE sequence (herein sharing 99.7% homology with SEQ ID NO: 4) can affect the protease activity, mRNA transcript, and subcellular localization of said protein (pp. 12).

17. Regarding derivatives and fragments of SEQ ID NO: 3 and SEQ ID NO: 4, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the

protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495].

18. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein

structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying prophetic teachings to protein biochemistry as exemplified in the references herein.

20. Claims **151** and **155** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn to polypeptides having at least 95% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 4. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 4 and the isolated polynucleotide comprising the nucleic acid sequence set forth in SEQ ID NO: 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

26. Claims **154, 156, 159, 165, 168, and 169** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. The term "heterologous" in claims 154, 159, 165, 168, and 169 is a relative term which renders the claim indefinite. The term " heterologous" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the Specification and the prior art as to what the metes and bounds of "heterologous" are.

28. The term "stringent" in claim 156 is a relative term which renders the claim indefinite. The term "stringent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims **151-169** are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/17369 (30 March 2000) Gurney *et al.*

30. WO 00/17369 teaches a polypeptide that shares 100% sequence homology to SEQ ID NO: 4 thus meeting the limitations of claims 151-153 (sequence listing). WO 00/17369 teaches a polypeptide that shares 100% sequence homology to SEQ ID NO: 4 that includes the peptide

triplets DSG and DTG and forms lacking a transmembrane domain thus meeting the limitations of claim 151 (claim 44; pp. 21 lines 20-25). WO 00/17369 teaches a polypeptide that shares 100% sequence homology to SEQ ID NO: 4 that is operable linked to any one of several purification and labeling tags thus meeting the limitations of claim 154 (claims 55-57).

31. WO 00/17369 teaches a polypeptide that shares 100% sequence homology to SEQ ID NO: 3 which encodes a polypeptide that shares 100% sequence homology with SEQ ID NO: 4 as well as polynucleotides that hybridize to said SEQ ID NO thus meeting the limitations of claims 155-158 (sequence listing; pp. 20 lines 20-25; pp. 22 lines 27-33). WO 00/17369 teaches a polynucleotide that shares 100% sequence homology to SEQ ID NO: 3 that includes the peptide triplets DSG and DTG and forms lacking a transmembrane domain thus meeting the limitations of claim 155 (claim 1; pp. 21 lines 20-25). WO 00/17369 teaches a polypeptide that shares 100% sequence homology to SEQ ID NO: 4 that is operable linked to any one of several purification and labeling tags, is in a vector, with expression control sequence (i.e. a promoter), and is in a host cell thus meeting the limitations of claims 159-169 (claims 1-14, 42, 43; pp. 12; pp. 24 lines 12-20).

Summary

32. Claims **151-169** are hereby rejected.

33. The following articles, patents, and published patent applications were found by the Examiner during the prior art search and are here made of note:

a. US 6361975 B1 (26 March 2002) Christie *et al.* (discloses a sequence with 96.9% sequence homology to SEQ ID NO: 4) {**IDS A43**}

b. US 6319689 B1 (20 November 2001) Powell *et al.* (discloses sequences with 98.2% sequence homology to SID: 3 and 99.5% sequence homology to SEQ ID NO: 4) **{IDS A39}**

c. US Patent Application Publication US 2002/0049303 A1 (25 April 2002) Tang *et al.* (discloses sequences with 97.1% sequence homology to SEQ ID NO: 3 and 96.9% sequence homology to SEQ ID NO: 4)

d. US Patent Application Publication US 2002/0164760 A1 (7 November 2002) Lin *et al.* (discloses sequences with 97.1% sequence homology to SEQ ID NO: 3 and 96.9% sequence homology to SEQ ID NO: 4)

e. Lin *et al.* (15 February 2000) "Human aspartic protease memapsin 2 cleaves the β-secretase site of β-amyloid precursor protein." PNAS **97**(4): 1456-1460 (discloses a sequence with 99.7% sequence homology to SEQ ID NO: 4)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
August 29, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER